Association of seasonal viral acute respiratory infection with pneumococcal disease

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Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies

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ABSTRACT

Objective Animal and in vitro studies suggest that viral acute respiratory infection (VARI) can predispose to pneumococcal infection. These findings suggest that the prevention of VARI can yield additional benefits for the control of pneumococcal disease (PD). In population-based studies, however, the evidence is not in accordance, possibly due to a variety of methodological challenges and problems in these studies. We aimed to summarise and critically review the methods and results from these studies in order to inform future studies.

Methods We conducted a systematic review of population-based studies that analysed the association between preceding seasonal VARI and subsequent PD. We searched MEDLINE, Embase and Global Health databases using tailored search strategies.

Results A total of 28 studies were included. After critically reviewing the methodologies and findings, 11 studies did not control for seasonal factors shared by VARI and PD. This, in turn, could lead to an overestimation of the association between the two illnesses. One case–control study was limited by its small sample size (n case=13). The remaining 16 studies that controlled for seasonal factors suggested that influenza and/or respiratory syncytial virus (RSV) infections were likely to be associated with the subsequent occurrence of PD (influenza: 12/14 studies; RSV: 4/5 studies). However, these 16 studies were unable to conduct individual patient data-based analyses. Nevertheless, these studies suggested the association between VARI and subsequent PD was related to additional factors such as virus type and subtype, age group, comorbidity status, presentation of PD and pneumococcal serotype.

Conclusions Population-based studies do not give consistent support for an association between preceding seasonal VARI and subsequent PD incidence. The main methodological challenges of existing studies include the failure to use individual patient data, control for seasonal factors of VARI and PD, or include other factors related to the association (eg, virus, age, comorbidity and pneumococcal serotype).

Strengths and limitations of this study

- This is the first review that critically reviewed the methods and findings of population-based studies that reported an association between viral acute respiratory infection and pneumococcal disease.
- Results of studies summarised according to study design and methods.
- No meta-analysis was conducted due to a variety of study designs, data sources and analytical methods in the studies so a narrative summary of the methods and results is provided.

INTRODUCTION

Both viral acute respiratory infection (VARI) and pneumococcal disease (PD) account for a substantial disease burden worldwide, especially in young children and the elderly.[1–3] The association of VARI and subsequent PD was not well recognised until the catastrophic 1918 influenza pandemic, which resulted in an estimated 40–50 million deaths[4]; it has been suggested that pneumococcus may have been a major cause of death.[5] Most recently, it was observed that the incidence of PD was higher during 2009 influenza H1N1 pandemic period than the same period in prepandemic[6–10] and postpandemic years.[7 9 10]

During interpandemic periods, the associations of seasonal influenza and other seasonal respiratory viruses such as respiratory syncytial virus (RSV), human metapneumovirus and parainfluenza virus (PIV) with PD incidence are poorly understood and remain unclear. In animal and in vitro studies, it has been suggested that viral respiratory infection could predispose to pneumococcal infection and might facilitate pneumococcal transmission; in turn, this coinfection could induce a lethal synergism that is much more severe than infection with either pathogen alone (a brief summary of findings is displayed in online supplementary Table S1). However, these studies are all relatively small-scale studies and may be subject to publication bias favouring reporting of positive findings. In

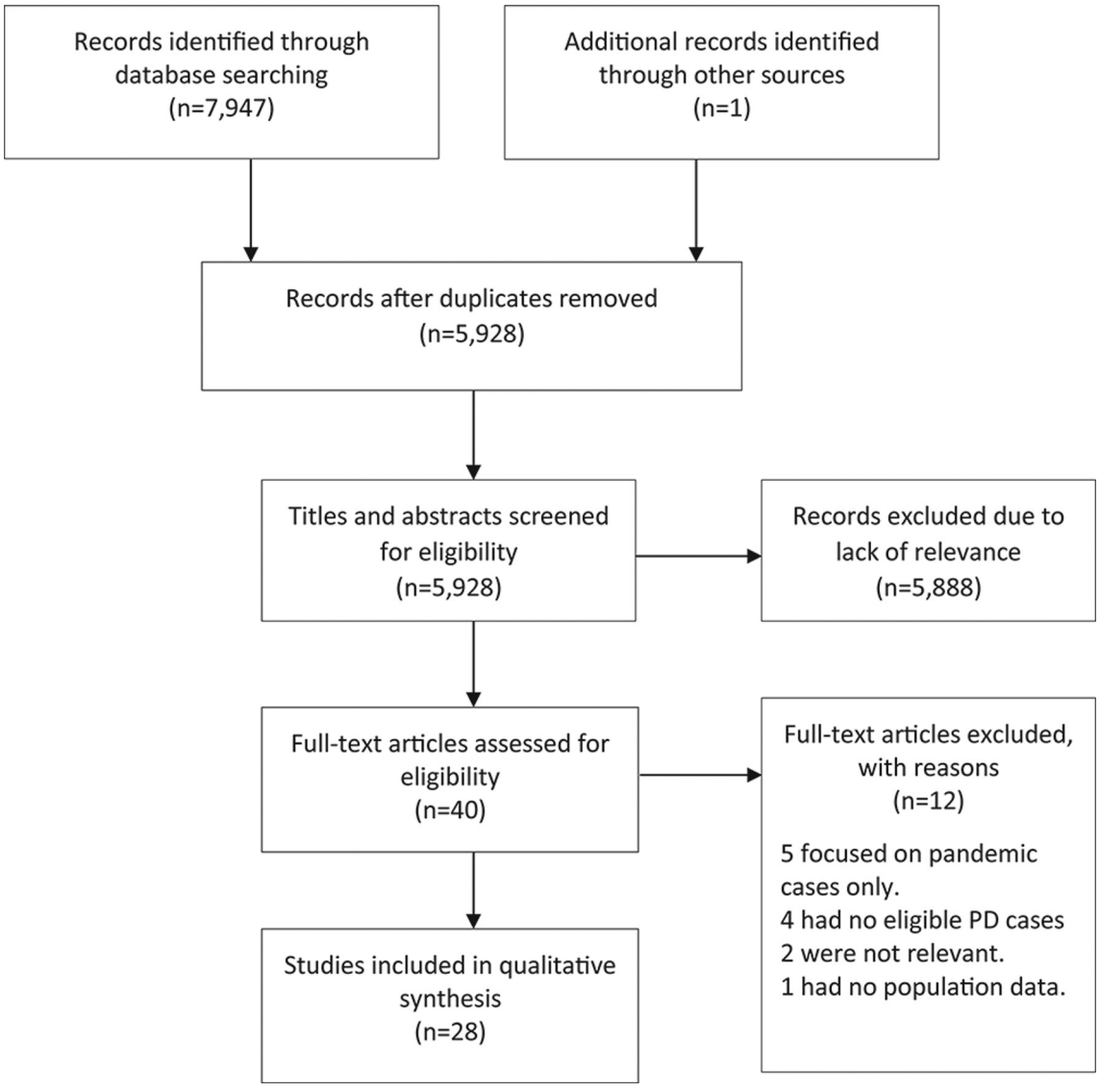

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the literature search. PD, pneumococcal disease.

population-based studies, the findings were inconsistent. These studies differed substantially in study design, data sources and methods, making it difficult to compare and interpret the results across the studies. We conducted a systematic review of population-based studies on the association of preceding VARI on the occurrence of PD to summarise the methodology and results, critically review the findings and present recommendations for future studies.

METHODS

Search strategy and selection criteria

We searched MEDLINE, Embase and Global Health databases using tailored search strategies (search strategies in online supplementary Text S1, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart in figure 1). We restricted the search to studies published between 1 January 1990 and 31 December 2017. We included population-based studies with clinically diagnosed PD cases (see next for detailed definition). In terms of VARI exposure, we accepted the following studies: (1) those with laboratory-confirmed viral infections; (2) those with the International Classification of Diseases (ICD) code for influenza and/or RSV infection and (3) those with case definition of influenza-like illness (ILI) and bronchiolitis as proxies for influenza and RSV, respectively. We excluded animal studies and theoretical studies where no population data were applied. We focused our review on the association of seasonal VARI and PD and thus excluded studies that reported pandemic influenza cases only. No language restrictions were applied. The reference lists of eligible studies were also checked to identify additional studies for inclusion. For all included studies, quality assessment was conducted using tailored Critical Appraisal Skills Programme checklists for case–control studies and

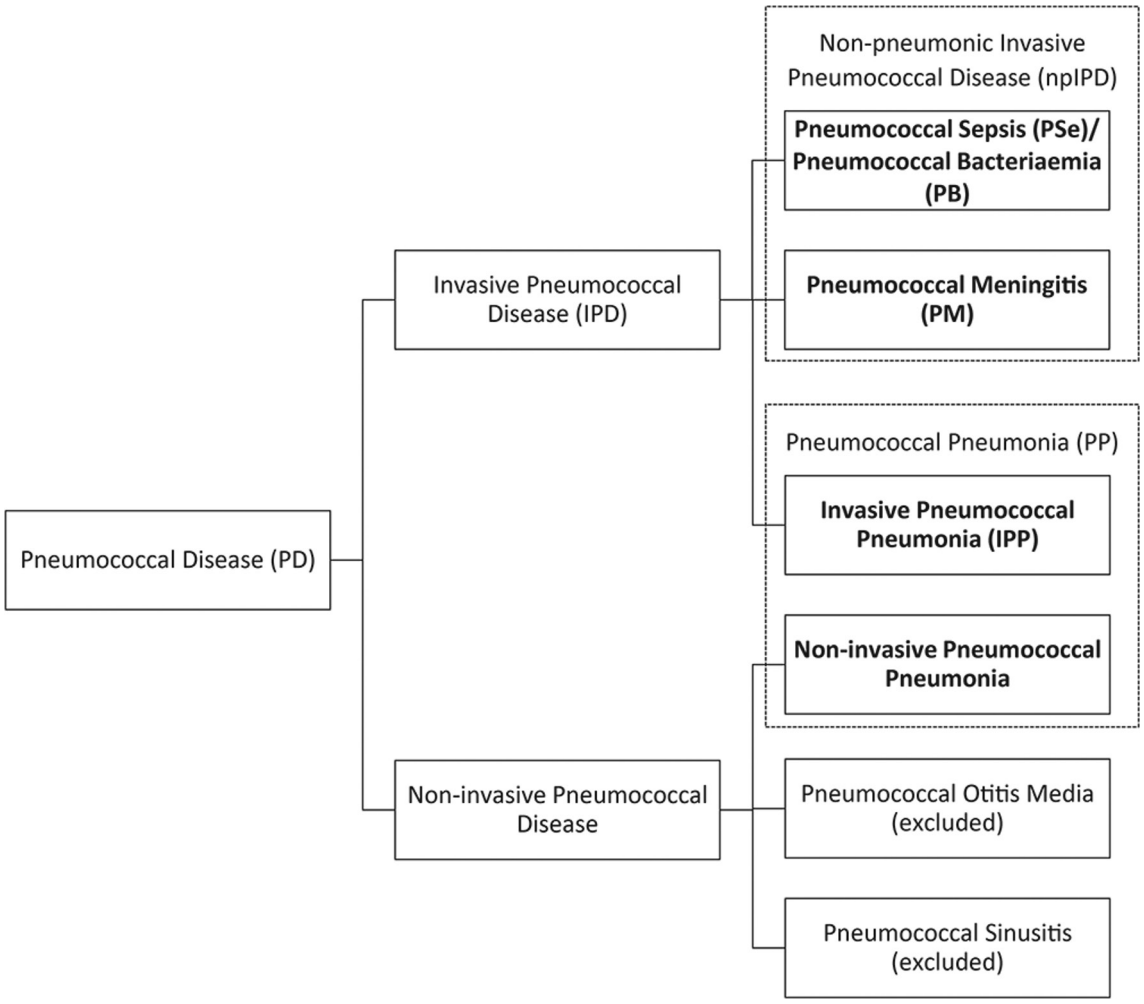

Figure 2 Category of pneumococcal disease in the present review.

cohort studies (online supplementary File S1). The review was conducted and reported according to the PRISMA guidelines (online supplementary File S2). The protocol for this systematic review was registered on PROSPERO (registration number: CRD42017064760; online supplementary File S3).

Definition of PD

We defined PD as any disease caused by *Streptococcus pneumoniae* (pneumococcus). Since this definition contains a broad range of diseases and symptoms, including some that are trivial to our review, we adopted a narrower definition. This narrowed definition includes invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP). We defined IPD as detection of pneumococcus in typical sterile sites (eg, blood, pleural and cerebrospinal fluid). A detailed category of PD for our review is displayed in figure 2. Additionally, we used the term 'non-pneumonic invasive pneumococcal disease (npIPD)', which referred to all IPD without diagnosis of pneumonia, in order to differentiate from both invasive and non-invasive PP.

Definition of VARI

We defined VARI as a respiratory tract infection with viral aetiology. ILI was viewed as a proxy for influenza infection in the present review. We defined ILI as a symptomatic cough and fever ≥38°C with onset within 7 days.

Data extraction

We used a standardised data extraction template to extract relevant data from the eligible full-text studies, including study design, data source, methods, results and conclusion. The principle summary measures of the association between VARI and PD include correlation coefficients, risk ratios, rate ratios, ORs and attributable percentage of PD to VARI. YL and MP independently extracted the data. HN or HC arbitrated any disagreement with the extraction.

Data analysis

Since it was expected that methodology would differ substantially between studies and a quantitative meta-analysis would not be appropriate, a narrative synthesis was conducted. Studies were summarised according to methodology to allow for more appropriate comparisons of the results.

In addition, because of the concern of multiple testing, we determined the number of tests conducted in each study, so a Bonferroni correction could be applied where applicable; only the tests relevant to the association

Table 1 Summary of individual patient data-based studies

Study	Study period	Population	VARI	PD (cases (n))	Methods	Main findings
Edwards *et al*[17]	2005–2009	All ages Northern Territory, Australia	IFV	IPD (n=346)	Using data from notifiable diseases system, relative risk (RR) of IPD calculated in ≤4 w after IFV compared with background risk	RR=112.5 (48.9–224.8)
O'Brien *et al*[25]	1995–1996	<18 y Iowa, USA	ILI IFV A	Severe PP (n=13)	Case–control design: case from children with severe PP, three controls per case selected, from friends of cases or from the same primary care practice, matched by age (within 1 y of the case). ILI history (7–28 d within admission) investigated by telephonic interview and IFV A convalescent serology collected.	OR (ILI history)=12.4 (1.7–306), OR (IFV A convalescent serology)=3.7 (1.0–18.1)
Stensballe *et al*[29]	1996–2003	All ages Denmark	RSV non-RSV	IPD (n=7787)	Prospective cohort study: two exposure groups, RSV and non-RSV respiratory infection hospitalisations within 30 d	RR for RSV=7.1 (3.6–14.3), RR for non-RSV=4.5 (2.0–10.0)

d, day(s); IFV, influenza virus; ILI, influenza-like illness; IPD, invasive pneumococcal disease; PD, pneumococcal disease; PP, pneumococcal pneumonia; RSV, respiratory syncytial virus; VARI, viral acute respiratory infection; w, week(s); y, year(s).

between VARI and pneumococcal infection were included as part of the correction. The Bonferroni-adjusted significance level was calculated as 0.05 divided by the number of relevant statistical tests within a study.

Patient and public involvement

No patients or public were involved in the present study.

RESULTS

A total of 28 studies[11–38] were eligible and included in the review. We noticed a variety of study designs, exposures and outcomes of interest and analytical methods in these studies (summarised in online supplementary Table S2). Due to the variety, we summarised the studies and displayed the results according to study design and methods.

Individual patient data-based studies

Individual patient data-based studies during the interpandemic period are sparse. Only three studies[17 25 29] were identified (table 1), including two cohort studies[17 29] and one small case–control study by O'Brien *et al*.[25] The reported results consistently supported the role of preceding VARI on the occurrence of PD. However, the two cohort studies did not attempt to control the seasonal risk factors of VARI and PD that could potentially bias the estimated effect size.

ECOLOGICAL STUDIES

In our review, 25[11–16 18–24 26–28 30–38] of the 28 studies were ecological studies. 16[11 13 14 16 18 19 21–24 26 32–38] out of the 25 ecological studies controlled for seasonal patterns of VARI and PD (online supplementary Table S2). Additionally, the study by Stensballe *et al*[29] analysed data at both population and individual levels but did not control for the seasonal patterns.

Correlation analyses with no control for seasonal patterns

Table 2 shows a summary of 11 studies[12–14 20 21 23 24 27 29 30 33] using correlation analyses without controlling for seasonal patterns of VARI and PD. Since all studies conducted multiple tests in analysing the correlation (eg, across age groups, viruses and lag time between VARI and PD), the Bonferroni method was applied to adjust the significance level. The correlation between PD and influenza or RSV was statistically significant in all five studies[14 23 24 29 30] that analysed population data of all ages (correlation coefficient r: 0.40–0.71 for influenza at no time lag, 0.47–0.77 for RSV at no time lag).

Regression analyses controlling for seasonal patterns

Table 3 shows the summary of the 15 studies[11 13 14 16 18 22–24 26 32 34–38] that controlled for seasonal patterns by regression analysis. Results were inconsistent among the studies. In all-age population studies, preceding influenza infection was likely to be associated with IPD (12 studies[13 14 16 18 22–24 32 35–38] reported an association and two studies[11 34] reported no association). According to two studies[23 24] that reported age-stratified results, the association between influenza and IPD was more likely to exist among older people than among young children. In terms of preceding RSV infection, four[14 24 34 37] out of five studies[14 23 24 34 37] observed an association of RSV with PD incidence. Specifically, one study[14] found the association between RSV and IPD only existed among children<5 years. Studies reporting other viruses such as ADV and PIV were sparse (two[14 23] and one[23] studies, respectively). Five studies[14 23 24 34 37] that reported two or more viruses demonstrated that the association differed by the type of

Table 2 Summary of ecological studies using correlation analysis

Study	Study period	Population	VARI	PD (cases (n))	Data sources and scale for analysis	Correlation method	Correlation coefficients (time lag)
Ampofo *et al*[12]	2001–2007	<18 y Utah, USA	IFV RSV PIV ADV hMPV	IPD (n=435)	Hospitalisation and laboratory data, fortnightly	Pearson	<18 y, IPD coded by ICD-9 IFV: **0.23c** (0), **0.24c** (2 w), **0.18c** (4 w); RSV: **0.31a** (0), **0.35a** (2 w), **0.34a** (4 w); PIV: 0.03 (0), –0.01 (2 w), –0.03 (4 w); ADV: 0.01 (0), –0.05 (2 w), –0.08 (4 w); hMPV: **0.31a** (0), **0.39a** (2 w), **0.37a** (4 w) (similar results for culture-confirmed IPD)
Burgos *et al*[13]	1996–2012	≥18 y Barcelona, Spain	IFV	IPD (n=1150)	Hospitalisation and surveillance laboratory data, monthly	Spearman	≥18 y IFV: **0.65a** (0), **0.45a** (1 m)
Ciruela *et al*[14]	2006–2012	All ages Catalonia, Spain	IFV RSV ADV	IPD (n=8044)	Microbiological reporting system, monthly	Spearman	All ages IFV: **0.71a** (0), **0.64a** (1 m); RSV: **0.77a** (0), **0.80a** (1 m); ADV: **0.61a** (0), **0.39a** (1 m) (similar results for age-stratified analysis of IFV and RSV; results of ADV were only significant among <5 y with no lag)
Jansen *et al*[20]	1997–2003	All ages Netherlands	IFV RSV	IPD (n=7266; PM+PB)	Weekly sentinel system, weekly	Spearman	0–4 y, 5–17 y, ≥18 y IFV-PB: **0.24b**, **0.21b**, **0.62b** IFV-PM: **0.23b**, **0.14b**, **0.39b** RSV-PB: **0.29b**, **0.12b**, **0.59b** RSV-PM: **0.36b**, –, **0.44b**
Kim *et al*[21]	1990–1993	All ages Houston, Texas, USA	IFV RSV ADV PIV non-IFV	IPD (n=480)	Hospitalisation and surveillance laboratory data, fortnightly	Pearson	≥18 y IFV: **0.46a** (0), **0.35c** (4 w) RSV: **0.56a** (0), **0.54a** (4 w) ADV: **0.25c** (0), **0.29c** (4 w) non-IFV: **0.38a** (0), **0.35c** (4 w) <18 y IFV: 0.08 (0), **0.23c** (4 w), **0.47a** (8 w) RSV: 0.13 (0), **0.28c** (4 w), **0.32c** (8 w) ADV: **0.31c** (0), **0.55a** (4 w), **0.24c** (8 w) non-IFV: **0.24c** (0), **0.39a** (4 w), **0.21c** (8 w)
Murdoch and Jennings[23]	1995–2006	All ages Christchurch, New Zealand	IFV RSV ADV PIV	IPD (n=737)	Surveillance data, monthly	Spearman	All ages IFV A: **0.44a** (0), **0.37a** (1 m) IFV B: **0.23c** (0), 0.13 (1 m) RSV: **0.52a** (0), **0.47a** (1 m) ADV: **0.27a** (0), **0.33a** (1 m) PIV 1/2: **0.24c** (0), **0.31a** (1 m) PIV 3: **0.34a** (0), **0.17c** (1 m) (correlations were stronger in 5–65 y and >65 y)
Nicoli *et al*[24]	1996–2009	All ages England and Wales, UK	IFV RSV	IPD (n=71 333)	Surveillance data, weekly	Pearson and Spearman	All ages, Pearson IFV: **0.54a** RSV: **0.47a** All ages, Spearman IFV: **0.67a** RSV: **0.63a** (correlations were stronger in 15–64 y and ≥65 y than 0–4 y and 5–14 y)

Continued

Table 2 Continued

Study	Study period	Population	VARI	PD (cases (n))	Data sources and scale for analysis	Correlation method	Correlation coefficients (time lag)
Peltola *et al*[27]	1995–2007	<5 y Finland	RV EV RSV IFV PIV ADV	IPD (about 90 cases per year)	National infectious disease register+3 studies+virus database, fortnightly	Pearson	<5 y RV: **0.28c**, **0.25c**, 0.31, **0.23a** (from four studies) EV: **0.17c** RSV: 0.05 IFV: −0.03 IFV A: −0.08 PIV: 0.02 ADV: −0.05
Stensballe *et al*[29]	1996–2003	All ages Denmark	RSV non-RSV	IPD (n=7787)	Population-based registries cohort, monthly	Pearson	All ages RSV: **0.55a** non-RSV: **0.65a** <2 y RSV: 0.08
Talbot *et al*[30]	1995–2002	All ages Tennessee, USA	IFV RSV	IPD (n=4147)	Surveillance data, weekly	Pearson	All ages RSV: **0.56a** (0), **0.60a** (1 w), **0.59a** (2 w), **0.57a** (3 w), **0.55a** (4 w) IFV: **0.40a** (0), **0.41a** (1 w), **0.34a** (2 w), **0.33a** (3 w), **0.26a** (4 w) (correlations were stronger in ≥18 y than <18 y)
Watson *et al*[33]	2000 (May–October)	All ages New South Wales, Australia	IFV RSV PIV	IPD (n=681)	Surveillance data, weekly	Pearson	<18 y IFV: not significant RSV: **0.58a** PIV: **−0.40c** ≥18 y IFV: not significant RSV: not significant PIV: not significant RSV or IFV: **0.48c**

Time lag indicates the time difference between preceding VARI and subsequent PD incidence.
Correlation coefficients in bold were statistically significant as originally reported in the study (p<0.05); correlation coefficients ending with 'a' were statistically significant after Bonferroni adjustment (p<0.05/number of relevant tests) or when the Bonferroni correction was deemed unnecessary; correlation coefficients ending with 'b' did not have enough information to apply the Bonferroni correction; correlation coefficients ending with 'c' were not statistically significant after Bonferroni adjustment.
ADV, adenovirus; EV, enterovirus; IFV, influenza virus; IPD, invasive pneumococcal disease; m, month(s); MPV, metapneumovirus; PB, pneumococcal bacteraemia; PD, pneumococcal disease; PIV, parainfluenza virus; PM, pneumococcal meningitis; RSV, respiratory syncytial virus; RV, rhinovirus; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Table 3 Summary of ecological studies controlling for seasonal patterns

Study	Study period	Population	VARI (unit used in model)	PD (cases (n))	Data sources and scale for analysis	Statistical methods	Covariates	RR (95% CI) (time lag)	AP (95% CI) (time lag)
Allard *et al*[11]	1997–2008	All ages Montreal, Canada	IFV (case)	IPD (n=2920)	Notification data and sentinel surveillance data, weekly	Negative binomial regression	Long-term trends and seasonal trends of IPD	All ages IFV A: 1.01 (0), 1.00 (1 w), 1.00 (2 w), 0.99 (3 w), 1.00 (4 w), 1.00 (5 w) IFV B: 1.01 (0), 1.01 (1 w), 1.00 (2 w), 1.01 (3 w), 0.99 (4 w), 1.01 (5 w)	
Burgos *et al*[13]	1996–2012	≥18 y Barcelona, Spain	IFV (IR per 1000)	IPD (n=1150)	Hospitalisation and surveillance laboratory data, monthly	Negative binomial regression	Temperature	≥18 y IFV: **1.23a** (1.03 to 1.47)	
Ciruela *et al*[14]	2006–2012	All ages Catalonia, Spain	IFV RSV ADV (IR per 100 000)	IPD (n=8044)	Microbiological reporting system, monthly	Negative binomial regression	Temperature >17°C	All ages IFV: **1.26b** (1.03 to 1.54) (0), 1.09 (0.87 to 1.36) (1 m) RSV: 1.15 (0.89 to 1.48) (0), **1.81b** (1.36 to 2.41) (1 m) ADV: 1.58 (0.88 to 2.74) (0), 1.32 (0.68 to 2.42) (1 m) <5 y IFV: 1.16 (0.90 to 1.50) (0), 1.06 (0.80 to 1.42) (1 m) RSV: 1.41 (1.00 to 1.97) (0), **2.57b** (1.78 to 3.71) (1 m) ADV: **2.47b** (1.38 to 4.53) (0), 1.00 (0.59 to 1.68) (1 m) (not significant in 5–64 y or≥65 y)	
Domenech de Cellès *et al*[16]	2000–2014	All ages France	ILI (as a proxy for IFV)	IPD (n=64 542)	National surveillance system, weekly	Mixed-effect linear regression	Seasonal trends of IPD		All ages ILI: median 4.9% across all study years (1 w)
Grabowska *et al*[18]	1994–2004	All ages Sweden	IFV (binary)	IPD (n=11 637)	Surveillance data, weekly	Negative binomial regression	Yearly trends and seasonal trends of IPD	All ages IFV: 1.03 (0.93 to 1.15) (0), 1.11 (1.00 to 1.23) (1 w), 1.11 (0.99 to 1.22) (2 w), **1.14c** (1.02 to 1.26) (3 w), **1.12c** (1.01 to 1.23) (4 w)	All ages **6%c** (1% to 12%) (3 w)
Kuster *et al*[22]	1995–2009	All ages Toronto/ Peel area, Canada	IFV (100 cases)	IPD (n=6191)	Population-based surveillance, weekly	Negative binomial regression	Multiyear trends and seasonal trends of IPD, relative humidity, temperature, UV Index	All ages IFV A&B: **1.09a** (1.05 to 1.14) (1 w), **0.93c** (0.89 to 0.98) (3 w) IFV A: identical to IFV A&B IFV B: not significant	
Murdoch and Jennings[23]	1995–2006	All ages Christchurch, New Zealand	IFV RSV ADV PIV (binary)	IPD (n=737)	Surveillance data, monthly	Negative binomial regression	Average daily temperature<10°C, PM10>50μg/m^3, days with rainfall>10, mean daily 09:00 humidity>75%, mean daily sunshine>6 hour	All ages IFV: **1.38c** (1.02 to 1.85) (0), 1.20 (0.91 to 1.58) (1 m) RSV: 1.15 (0.87 to 1.52) (0), 0.90 (0.68 to 1.18) (1 m) PIV 1/2: 1.04 (0.82 to 1.30) (0), 1.04 (0.84 to 1.29) (1 m) PIV three outside IFV season: **1.64a** (1.18 to 2.30) (0), **1.49c** (1.07 to 2.08) (1 m) ADV: 0.97 (0.78 to 1.20) (0), **1.26c** (1.02 to 1.54) (1 m) (similar in 5–65 y, >65 y; not significant in <5 y)	
Nicoli *et al*[24]	1996–2009	All ages England and Wales, UK	IFV RSV (case)	IPD (n=71 333)	Surveillance data, weekly	Negative binomial regression	Weekly temperature or monthly hours of sunshine (separately in models; results were similar)		All ages, 0–4 y, 5–14 y, 15–64 y, ≥65 y controlling for temperature, multiplicative model IFV: **5.6%b** (0.2% to 23.8%), −0.4% (−1.8% to 0.0%), **2.9%c** (0.0% to 13.6%), **1.8%c** (0.1% to 7.4%), **3.2%b** (0.0% to 14.7%) RSV: **2.9%b** (0.1% to 14.2%), **1.4%c** (0.0% to 6.9%), **5.9%b** (0.0% to 27.6%), **14.5%b** (0.0% to 52.7%), **7.9%b** (0.0% to 27.4%) (no significant results in time lag analyses)
Opatowski *et al*[26]	2001–2004	All ages France	VARI (IR)	PM (n=1383)	Surveillance data, weekly	Poisson regression using generalised estimating equations approach	Seasonal trends of PM	All ages regression parameter: **19.4c** **23.1a** (1 w) **23.9a** (2 w)	

Continued

Table 3 Continued

Study	Study period	Population	VARI (unit used in model)	PD (cases (n))	Data sources and scale for analysis	Statistical methods	Covariates	RR (95% CI) (time lag)	AP (95% CI) (time lag)
Walter *et al*[32]	1995–2006	All ages USA	IFV (positive percentage)	IPD (IPP, nplPD; n=21 239)	Surveillance data, weekly	Negative binomial regression	Seasonal trends and linear trends of IPP		Northeast, all ages IFV-IPP: **4.9%c** (4.5% to 5.3%) (1 w) South, all ages IFV-IPP: **5.4%b** (5.0% to 5.9%) (1 w) West, all ages IFV-IPP: **5.2%c** (4.8% to 6.0%) (1 w) (not significant for IFV-nplPD)
Weinberger *et al*[34]	1996–2012	<7 y Navajo/White Mountain Apache population, USA	Bronchiolitis (IR, as a proxy for RSV) IFV (IR)	IPD (IPP, nplPD; n=496)	Four community-based studies, monthly	Poisson regression	Pneumococcal carriage prevalence, seasonal trends of IPD, PCV periods		<7 y Bronchiolitis-PP: **15.5%b** (1.8% to 26.1%) Bronchiolitis-nplPD: 8.0% (–4.8% to 19.3%) (not significant for IFV)
Weinberger *et al*[35]	1977–2007	≥40 y Denmark	ILI (case, as a proxy for IFV)	IPP (n=8308)	Surveillance data+nationwide general practice reports, weekly	Poisson regression	Seasonal trends of IPP, dummy variable for weeks 1, 2, 3, 51, 52 and its interaction with ILI		≥40 y, low comorbidity and low serotype invasiveness ILI: **17.9%a** (13.6% to 21.9%) (1 w) ≥40 y, low comorbidity and high serotype invasiveness ILI: **6.7%a** (3.8% to 11.7%) (1 w) ≥40 y, medium/high comorbidity and low serotype invasiveness ILI: 1.3% (–1.6% to 5.4%) (1 w) ≥40 y, medium/high comorbidity and high serotype invasiveness ILI: **8.9%a** (6.6% to 11.8%) (1 w)
Weinberger *et al*[36]	1977–2007	All ages Denmark	ILI (case, as a proxy for IFV)	IPD (IPP, nplPD; n=13 882)	Surveillance data+nationwide general practice reports, weekly	Poisson regression	Seasonal trends of IPD, dummy variable for weeks 1, 2, 3, 51, 52 and its interaction with ILI		15–39 y, low comorbidity ILI-IPD: **9.9%a** (6.0% to 13.0%) (1 w) ILI-IPP: **11.2%a** (6.5% to 14.8%) (1 w) ILI-nplPD: 6.6% (–1.2% to 14.3%) (1 w) 15–39 y, medium/high comorbidity ILI-IPD: 0.3% (–8.4% to 9.7%) (1 w) ILI-IPP: 5.4% (–5.0% to 18.7%) (1 w) ILI-nplPD: –6.6% (–25.7% to 7.6%) (1 w) ≥40 y, low comorbidity ILI-IPD: **7.6%a** (5.1% to 11.6%) (1 w) ILI-IPP: **7.8%a** (5.8% to 11.7%) (1 w) ILI-nplPD: **6.9%a** (1.8% to 12.8%) (1 w) ≥40 y, medium/high comorbidity ILI-IPD: **6.2%a** (4.3% to 9.3%) (1 w) ILI-IPP: **6.5%a** (4.4% to 10.1%) (1 w) ILI-nplPD: **5.3%a** (2.5% to 8.9%) (1 w)
Weinberger *et al*[37]	1992–2009	<2 y 36 states in USA	IFV RSV (IR)	PD (PP, PSe; n=17 404)	State inpatient databases, weekly	Poisson regression	Seasonal trends of PD, PCV periods, IFV or RSV, state	0–2 m, 3–11 m, 0–11 m, 12–23 m RSV-PP: **1.42b** (1.30 to 1.55), **1.24b** (1.17 to 1.33), **1.23b** (1.19 to 1.30), **1.12b** (1.09 to 1.18)	0–2 m, 3–11 m, 0–11 m, 12–23 m IFV-PP: 2.1% (–4.5% to 1.4%), **2.2%a** (0.1% to 3.4%], 0.6% (–0.9% to 1.4%), **3.2%a** (1.7% to 4.7%) RSV-PP: **35.7%a** (27.9% to 42.7%), **20.0%a** (14.7% to 24.8%), **20.3%a** (17.4% to 25.1%), **10.1%a** (7.6% to 13.9%) IFV-PSe: 0.7% (–1.1% to 2.2%), **–2.7%a** (–3.7% to –1.7%), –0.6% (–1.4% to 0.3%), **1.9%a** (1.1% to 2.6%) RSV-PSe: **15.0%a** (13.1% to 17.1%), 0.1% (–4.9% to 5.0%), **7.2%a** (5.3% to 9.0%), **3.8%a** (2.5% to 5.2%)

Continued

Table 3 Continued

Study	Study period	Population	VARI (unit used in model)	PD (cases (n))	Data sources and scale for analysis	Statistical methods	Covariates	RR (95% CI) (time lag)	AP (95% CI) (time lag)
Zhou *et al*[38]	1994–2005	All ages Atlanta, USA	IFV RSV (positive percentage)	IPP (n=5683)	Surveillance data, weekly	Negative binomial regression (comparison between models with and without IFV and RSV)	Temperature, sunshine, precipitation	P values for the likelihood ratio test were <0.05 for 5 of 11 influenza seasons: 1994–1995, 1996–1997, 1998–1999, 2003–2004, 2004–2005; after Bonferroni adjustment association was significant for 3 of 11 influenza seasons: 1996–1997, 2003–2004, 2004–2005.	

Time lag indicates the time difference between VARI and subsequent PD incidence.
RR or attributable percentage in bold was statistically significant as originally reported in the study (p<0.05); RR or attributable percentage ending with 'a' were statistically significant after Bonferroni adjustment (p<0.05/number of relevant tests) or when the Bonferroni correction was deemed unnecessary, those ending with 'b' did not have enough information to apply the Bonferroni correction; RR or attributable percentage ending with 'c' were not statistically significant after Bonferroni adjustment.
ADV, adenovirus; AP, attributable percentage; CI, confidence interval; h, hour(s); IFV, influenza virus; ILI, influenza-like illness; IPD, invasive pneumococcal disease; IPP, invasive pneumococcal pneumonia; IR, incidence rate; npIPD, non-pneumonic invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PD, pneumococcal disease; PIV, parainfluenza virus; PP, pneumococcal pneumonia; PSe, pneumococcal sepsis; RR, relative risk; RSV, respiratory syncytial virus; UV Index, clear-sky ultraviolet index; VARI, viral acute respiratory infection; w, week(s); y, year(s).

virus. Moreover, the association could differ among virus subtypes (eg, influenza A vs influenza B[22] and PIV 1/2 vs PIV 3.[23] Notably, there are other factors that could influence the strength of the associations reported in these studies. For instance, the association could vary by presentation of PD (invasive PP, IPP vs npIPD[32 34 36] and PP vs pneumococcal sepsis (PSe))[37]; preceding VARI was more likely to be associated with the occurrence of pneumonia than other clinical presentations. Additionally, the results from studies in Denmark, where comorbidity status and pneumococcal serotype were available, demonstrated that influenza had a greater influence on the incidence of low-invasiveness serotypes than medium or high invasiveness among the low comorbidity group; among the high comorbidity group, the pattern was reversed.[35 36]

Studies using other analyses

Seven ecological studies[15 16 19 22 26 28 31] used other analytical methods (table 4). Except for studies by Hendriks *et al*[19] and Toschke *et al*,[31] all studies reported an association between VARI and PD.

DISCUSSION

In our review, we summarised population-based studies that evaluated the association of seasonal VARI and subsequent PD. To our knowledge, this is the first review that summarises the methodology and findings of existing epidemiological studies on this topic.

We found that reported associations between VARI and subsequent PD were inconsistent among the 28 included studies. Only three studies[17 25 29] analysed the association using individual patient data. The two cohort studies[17 29] did not account for the shared risk factors between VARI and PD that influenced their seasonality, substantially limiting the inferences that can be made from these data while the case–control study[25] was limited by its small sample size (n case=13). In ecological studies, only 16[11 13 14 16 18 19 22–24 26 32 34–38] of the 25[11–16 18–24 26–28 30–38] ecological studies accounted for seasonal patterns. In these studies, we found that influenza and/or RSV infections were likely to be associated with the subsequent occurrence of PD. For influenza, the association was stronger among younger populations compared with older adults[23 24] while the pattern was reversed for RSV.[14] Data from multiple studies suggested that virus type (five studies)[14 23 24 34 37] and subtype (two studies)[22 23], comorbidity status (two studies)[35 36] and pneumococcal serotype invasiveness (one study)[35] could influence the association. However, these 16 ecological studies had various population characteristics (eg, age, comorbidity, immunity status), PD datasets, VARI datasets and analytical methods. As such, heterogeneity among the studies, along with their ecological nature, limits the amount of valid inferences that can be made from the data (as summarised above).

Nevertheless, these studies provide important clues for the potential factors related to the association between

Table 4 Summary of ecological studies using other methods

Study	Study period	Population	VARI	PD (cases (n))	Data sources and scale for analysis	Methods	Main findings
Dangor *et al*[15]	2005–2008	<15 y Soweto, South Africa	IFV	IPD (n=636)	Hospitalisation and surveillance laboratory data, monthly	X-11 seasonal adjustment method to retain seasonal components. Peak timing compared by time series graph.	IFV peak in May–July, followed by IPD (August–October); no correlation analysis results reported
Domenech de Cellès *et al*[16]	2000–2014	All ages France	ILI (as a proxy for IFV)	IPD (n=64 542)	National surveillance system, weekly	Correlation analysis of waveforms of ILI and IPD	Correlation of peak timing of ILI and IPD peak 2: 0.42 (0.04 to 0.66); correlation of total cases of ILI and IPD: 0.31 (0.03 to 0.56)
Hendriks *et al*[19]	2004–2014	All ages Netherlands	ILI (as a proxy for IFV)	IPD (n=6572)	Surveillance data, weekly	Cross-correlations of the time series model (seasonal autoregressive integrated moving average, SARIMA) residuals	No significant cross-correlations observed
Kuster *et al*[22]	1995–2009	All ages Toronto/ Peel area, Canada	IFV	IPD (n=6191)	Population-based surveillance, weekly	Spearman correlation for phase and amplitude between IFV and IPD; Granger methods to test whether influenza predicted IPD; Case-crossover analysis to evaluate short-term associations	Phase and amplitude between IFV and IPD not correlated; Granger test of IFV causing IPD: p<0.001; case-crossover OR: 1.10 (1.02 to 1.18) at 1 w lag
Opatowski *et al*[26]	2001–2004	All ages France	VARI	PM (n=1383)	Surveillance data, weekly	Mathematic model of pneumococcus transmission, to estimate the interaction parameters between VARI and PM	Factor of VARI on pneumococcus acquisition or transmissibility: 8.7 (4.6 to 14.4); factor of VARI on pathogenicity: 92 (28 to 361)
Shrestha *et al*[28]	1989–2009	All ages Illinois, USA	IFV	PP (n not known)	Hospital data, weekly (dataset I from 1989 to 1997, dataset II from 2000 to 2013)	Mathematic model of pneumococcal pneumonia (PP) transmission, to estimate the interaction parameters between VARI and PP	Factor of IFV on PP susceptibility: dataset I 115 (70 to 200), dataset II 85 (30 to 160)
Toschke *et al*[31]	1997–2003	<16 y Germany	IFV A	IPD (n=1474)	Surveillance data, monthly	Multivariate time series analysis using '3 hour algorithm', which fit an autoregressive Poisson or negative binomial model to time series	IFV A season did not affect IPD season (p=0.49); IFV A peak did not precede IPD peak

IFV, influenza virus; ILI, influenza-like illness; IPD, invasive pneumococcal disease; PD, pneumococcal disease; PM, pneumococcal meningitis; VARI, viral acute respiratory infection; w, week(s); y, year(s).

VARI and subsequent PD, and thus could help with the conception and design of future studies. Ideally, in order to understand whether a particular preceding VARI can predispose an individual to PD, a prospective cohort study that monitors each individual for VARI and pneumococcal infection would be used, allowing analyses at both individual and population levels. However, such a design would not be feasible or affordable as inter alia pneumococcal infections are rare. Alternatively, the utilisation of large-scale routine health data and reliable data linkage (through unique individual identifiers) from sources such as surveillance data and hospitalisation datasets may be feasible in many industrialised countries. An example of such data linkage in our review is the study by Stensballe *et al*[29] that linked information from four Danish population-based registries. While the authors conducted individual-level analysis, the results were based on cases tested for both the presence of respiratory viruses and pneumococcal infection. The true number of VARI-associated PD cases is likely to be significantly higher due to incomplete testing of cases; the untested viral-pneumococcal cases could represent a crucial source of selection bias. Community-based active surveillance can likely address the issue of missing cases but such surveillance would be labour intensive and less cost effective to conduct. Another option is a case–control study, which is affordable and practical, but not without its limitations. In addition to challenges in designing such studies, defining the history of VARI is likely to be inaccurate since the timing of viral serology may be less accurate (information bias).[27] In the case–control study by O'Brien *et al*,[25] the authors used influenza-strain specific convalescent serology as evidence for preceding influenza infection. The authors also conducted telephone interviews to investigate ILI history but they did not mention whether interviewers and interviewees were blind to case or control status. Moreover, the value of this case–control study is limited by its very small sample size (n case=13).

Compared with individual patient data-based studies, ecological studies are more feasible, and thus the most common study design included in our review (25/28). However, there are some caveats when interpreting results from ecological studies. First, causality can never be inferred from such studies. Second, the results should be interpreted at a population level and cannot be generalised to the individual level. Since ecological studies used data aggregated into broad categories, the potential biases introduced by the aggregation should be taken into account. For instance, while 16 out of 25 ecological studies used weekly data, others used fortnightly or monthly data. This may lead to misclassification as the time window of the association of VARI on PD susceptibility can be as short as 1 week.[39 40] Moreover, data from different sources in ecological studies should represent the same population.

Apart from the study design, one further challenge of analysing the association is accounting for the influence of seasonal factors of VARI and PD (confounding). Both VARI and PD have similar seasonal patterns, and thus are likely to correlate as indicated by the correlation results from ecological studies. The increased risk of PD during an epidemic season could be caused by VARI or by seasonal risk factors or by both. In the present review, 11 studies[12 15 17 20 21 27–31 33] did not attempt to control for seasonal confounders, likely leading to biased estimations of the association. For example, the study by Edwards *et al*[17] reported a relative risk as high as 112.5 when not adjusting any seasonal factors. One way to address this problem in such studies would be to match the individuals with the onset timing of pneumococcal infection, keeping the risk of PD comparable between VARI cases and non-VARI cases; for ecological studies, regression analysis adding seasonal terms or climatic factors (such as temperature and humidity), or cross-correlation analysis of time series controlling for seasonal patterns could be considered.

Our review suggests that the association of VARI and subsequent PD could vary by virus type[14 23 24 34 35] and even by subtype.[22 23] Studies using combinations of viral infections such as all virus, influenza +RSV, non-influenza, or non-RSV could give biased estimations of the association. However, it is not always practical to analyse the association by virus type. In ecological studies, different types of viruses might cocirculate and thus be highly correlated in incidence, making it difficult to determine the role for each virus. In terms of PD, most studies used IPD as the outcome of interest. However, studies that categorised IPD into IPP and npIPD found that the association was more pronounced in IPP than in npIPD.[32 34 36] A similar finding, that the association was stronger in PP than PSe, was reported in another study.[37] These results suggest VARI is more likely to be associated with pneumonic pneumococcal infections than non-pneumonic infections. In our review, we excluded studies using information other than clinical diagnosis as a proxy for PD (eg, prescription data and carriage data). Pneumococcal carriage could have a fundamental role in the transmission and incidence of PD.[41] In a study analysing the impact of pneumococcal carriage and viral activity, Weinberger *et al*[34] found npIPD was associated with carriage prevalence, whereas IPP was associated with bronchiolitis (as a proxy for RSV). The authors also proposed that preceding VARI increased susceptibility but did not enhance transmission (indicated by carriage prevalence) in children. However, more studies are needed to confirm these findings.

The association could also vary by population characteristics. According to two studies that displayed age-stratified results,[23 24] the association of influenza and subsequent IPD was more likely to exist among older people than among young children. Studies by Weinberger *et al*[35 36] gauged the association in different comorbidity and pneumococcal serotype groups among Denmark populations. The results showed that influenza had a stronger impact on the incidence of low-invasiveness serotypes than medium or high invasiveness ones in the low comorbidity group, while the pattern reversed in the high

comorbidity group. Another study that analysed clinical records of 919 patients with PP found that infrequently colonising pneumococcal serotypes were more likely to cause PP after preceding VARI, particularly in patients with immunodeficiency or chronic lung diseases.[42] These findings suggest the need for future studies to analyse the association by age group, pneumococcal serotype and comorbidity status. Moreover, the recent introduction of pneumococcal vaccines has brought changes in the incidence of serotype-specific PD,[43] making the association of VARI and PD more complicated to understand. As a result, future studies should consider the possible serotype-specific influence that pneumococcal vaccines have on both individual immunity and herd immunity when analysing the association.

In addition to the factors discussed above, additional factors may influence the estimates of the association. The first is the change over time in the methodology of data collection, including changes in test method or diagnosis, clinical practice and health-seeking behaviour. The second is the possible delay in measurement, which happened most often in passive hospital-based studies. Third, for ecological studies using aggregated data, 'holiday spikes' could occur due to more social gatherings[44]; besides, weekends and holidays might influence timely tests or diagnosis as well as the health-seeking behaviour of patients.

To our knowledge, this is the first review to summarise and critically appraise the methods and results of population-based studies about the association between seasonal VARI and subsequent PD. However, this review is not without its limitations. First, due to a variety of study designs, data sources and analytical methods in the studies included, no meta-analysis was conducted in the review. As such, we were unable to provide a quantitative measure of the association of seasonal VARI and PD. Second, no unpublished data sources were included in the review, which could mean the data reported favours positive associations due to publication bias. Thus, caution should be taken when interpreting the results. Third, we found many studies tended to conduct multiple statistical tests using different subgroups and time periods (eg, age group, virus, time lag between VARI and PD) without specifying the primary study question a priori or making proper statistical adjustments to account for multiple testing. This could give rise to an increased risk of reporting false positive results. In this review, we applied Bonferroni corrections to adjust for the multiple tests where deemed necessary. Since the Bonferroni method is conservative and we are unable to adjust for studies where p values were not given, the adjustment in our review is intended for readers' reference and as caveats for future studies.

Given the substantial burden of VARI across the world,[1] even a modest association between VARI and subsequent PD could lead to a substantial burden of disease in terms of VARI-related PD cases. If proper antibacterial interventions could be applied to those with higher risk of PD due to a preceding VARI, subsequent pneumococcal infections could be prevented. The interventions would be more effective/better targeted if we could estimate the risk (ie, the strength of association) according to timing of infection by week/month of a year, age, comorbidity status, virus type and status of immunity. In turn, understanding the association between VARI and subsequent pneumococcal infection can help evaluate the full impact of viral vaccine programmes.

In conclusion, the role of seasonal VARI on subsequent PD incidence remains controversial in population-based studies. Nevertheless, these studies provide valuable information and can help with the conception of future well-designed studies. Future work could explore the association by timing of infection, age, comorbidity status, virus type, pneumococcal serotype and presentation, and thus would identify potentially susceptible populations with VARI for preventive interventions.

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